b.) Remarks

The Examiner has objected to claim 12 as containing an extra period (".") as noted at page 2 of the Office Action. Also, claims 7-12 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In response, the superfluous period has been deleted from claim 12 (and relocated in claim 7), and "method for stabilization" has been deleted from claims 7-12. Accordingly, this objection and rejection are overcome.

Claims 1, 6-8, 10 and 12 are rejected under 35 U.S.C. §103(a) as being obvious over Shimada (*Bioorganic & Medicinal Chemistry Letters*, Vol. 7, No. 18 (1997) 2349-52) in view of Sako (U.S. Patent No. 6,562,375), and claims 9-11 are rejected as being obvious over this art in view of Okuda (U.S. Patent No. 4,654,206).

Claims 1, 6-8, 10 and 12 are rejected as being obvious over Suzuki (U.S. Patent No. 5,484,920) in view of Shimada and Sako, and claims 9-11 are rejected as being obvious over this art in view of Okuda.

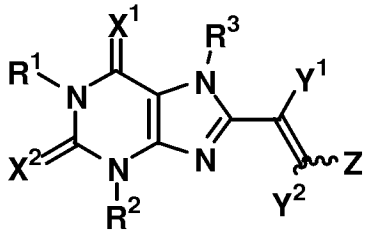
Lastly, claims 1, 6-8, 10 and 12 are rejected as being obvious over Hara (WO 01/32182) in view of Shimada and Sako, and claims 9-11 are rejected as being obvious over Hara in view of Shimada, Sako and Okuda.

According to the Examiner, the primary references of Suzuki, Hara and Shimada each teach 8-styrylxanthines of formula (IA). Shimada also shows dilute solutions of (E)-8-styrylxanthines rapidly isomerize when exposed to light. As to the secondary references, Sako teaches "changes in drug release" can be prevented by adding

yellow or red ferric oxide to matrix type sustained-release preparations containing polyethylene oxide. Okuda teaches a solid preparation of dihydropyridine coated with titanium dioxide and iron oxide.

This rejection is respectfully traversed. However, prior to setting forth their bases of traversal, Applicants would like to briefly discuss the salient features of the present invention and *inter alia*, its patentable novelty over the prior art.

As the Examiner is aware, the claimed invention is a method for suppressing dimerization of a xanthine compound (or pharmaceutically acceptable salt) in solid formulation, wherein the xanthine compound is represented by formula (IA)[1]



(IA)

Such is easily achieved according to the present invention by providing iron oxide in the solid formulation, wherein dimerization of the xanthine compound or salt is suppressed.

At the outset, Applicants respectfully wish to clarify that isomerization is not the same thing as dimerization, and results from a disparate process. Isomerization is a process whereby a compound is changed into an isomer, e.g., a compound having the same elemental composition but a different structure. McGraw-Hill Dictionary of Chemistry (1997) 207; Hawley's Condensed Chemical Dictionary 14th ed. (2001) 626. In contrast,

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[1] Wherein Y^1 and Y^2 are independently hydrogen, halogen or lower alkyl; Z is substituted or unsubstituted aryl or heteroaryl; R^1, R^2 and R^3 are independently hydrogen, lower alkyl, lower alkenyl or lower alkynyl; and X^1 and X^2 are oxygen or sulfur.

dimerization is the process that results in a chemical combination of two entities of the same species. McGraw-Hill Dictionary of Chemistry (1997) 119; Hawley's Condensed Chemical Dictionary 14th ed. (2001) 389-90. These are understood to be completely different results obtained through completely different mechanisms. Sorrell, ed., *Organic Chemistry* (1998) 124, 198.

In this regard, in Applicants' specification, Test Example 1 (page 37) and Table 1 (pages 38-39) show that isomerization of the subject xanthine compound is completely suppressed ("nd", for "none detected") by coating the xanthine compound with titanium oxide. However titanium oxides does not at all suppress dimerization of the xanthine compound (0.87%, where anything over just 0.1% is unacceptable). See Tablet 1 in Table 1. In contrast, dimerization of the xanthine compound is highly suppressed ($\leq$0.1%) by coating with ferric oxide (Tablets 2 ~ 6 in Table 1).

These results confirm isomerization and dimerization occur by different mechanisms. These results also confirm, at least for just that reason, those of ordinary skill understand isomerization inhibitors are not expected to inhibit dimerization.

Shimada teaches 8-strylxanthines in dilute solution rapidly isomerize when exposed to light. First, Shimada is unconcerned with stability of 8-styrylxanthines in solid formulation as claimed herein and, in any event, Shimada is also unconcerned with dimerization.

These deficiencies are not addressed by Sako or Okuda, as discussed below.

Sako teaches that changes in drug release from a preparation containing polyethylene oxide can be prevented by adding yellow or red ferric oxide. First, Sako

teaches the ferric oxide exhibits the photoactivity of polyethylene oxide, not the photoactivation of xanthine. However, the structures and chemistry of polyethylene oxide are quite different from Applicants' xanthine compounds. In any event, there is no relationship whatsoever between the mechanisms of photoactivity of polyethylene oxide and dimerization of xanthine compounds.

As to Okuda, first, it does not teach or suggest that iron oxide has any effect whatsoever on the stability of its dihydropyridine compounds. Even so, in any event, however, there is no relationship understood in the art between the mechanisms underlying photostability (or isomerization) of dihydropyridine and dimerization of Applicants' xanthine compound.[2] Haakins, ed., *Biotransformations* Vol. 7 (1996).

As to Suzuki and Hara, such are no more relevant than Shimada and so, their deficiencies are not overcome by Shimada, Sako or Okuda.

In view of the above amendments and remarks, Applicants respectfully submit that all of the Examiner's concerns are now overcome and the claims are now in allowable condition. Accordingly, reconsideration and allowance of this application is earnestly solicited.

Claims 1 and 6-12 remain presented for continued prosecution.

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[2] That xanthine compound, of course, is purine-based, not pyridine-based.

Applicants' undersigned attorney may be reached in our New York office by telephone at (212) 218-2100. All correspondence should continue to be directed to our below listed address.

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